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Background: Eradicating inhibitors to restore the effectiveness of Factor VIII (FVIII) is a desirable treatment goal for People with Severe Hemophilia A (PwSHA) and inhibitors, as this enables treatment of bleeding episodes with FVIII concentrates. However, since Immune Tolerance Induction (ITI) is a burdensome and costly treatment, it is important to identify determinants for ITI success to decide if it is worth undertaking ITI. For more effective treatment allocation, there is a need to identify which persons will or will not benefit from ITI. **Aim:** We aimed to identify determinants of successful ITI in PwSHA and to use these determinants in a clinical prediction model. **Methods:** German, Brazilian, Dutch, Canadian, and Italian PwSHA who underwent ITI were included. The primary outcome was clinical ITI success, defined by (1) a negative inhibitor titer, and (2) an adequate clinical response to FVIII concentrates. Clinical determinants included F8 genotype, race, age, cumulative exposure days to FVIII, inhibitor titers, and ITI regimen. Genetic determinants included in the analyses were FCGR gene, IL10 CA short tandem repeat, and gene variants. Crude Relative Risks (RR) were calculated for ITI success with 95% Confidence Intervals (95% CI). **Results:** In total, 224 PwSHA were included (61 German, 51 Brazilian, 45 Dutch, 39 Canadian, and 28 Italian). The median ages at inhibitor development and ITI start were 2-years (Interquartile Range [IQR 1–3]) and 2-years (IQR 1–6). The median interval between inhibitor diagnosis and ITI start was 17-weeks (IQR 2–64). Most ITI trials started with recombinant FVIII (130; 58%) and the median prescribed regimen at ITI start was 43 IU/kg/day (IQR 21–200). The need for adjuvant therapy and central venous access infection were related to failure, while inhibitor titer at detection < 10 BU/mL, inhibitor titer immediately before ITI start < 10 BU/mL, and peak inhibitor titer ever measured < 100 BU/mL were related to success. Inhibitor peak titer below 100 BU/mL showed the highest chance for ITI success (OR = 11.5, 95% CI 5.5–24.3, p < 0.001). **Conclusion:** Historical peak titer below 100 BU/mL was the strongest determinant for ITI success. Genetic analyses will be available by the due date, and we will develop a prediction model to estimate the chance of success.

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GENOMIC DIVERSITY AND ANCESTRY OF ADMIXED PATIENTS WITH HEMOPHILIA A AND INHIBITORS: INSIGHTS FROM WHOLE EXOME SEQUENCING IN THE BRAZILIAN IMMUNE TOLERANCE (BRAZIT) STUDY

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Hemophilia A is an X-linked bleeding disorder caused by mutations in the FVIII gene. BrazIT is a nationwide cohort of 193 patients that, developing neutralizing alloantibodies (inhibitors) against the first line treatment with exogenous FVIII, received Immunotolerance Treatment (ITI). Sixtyseven patients (35%) failed ITI, 62 (32%) achieved partial success, and 64 (33%) had complete success. We performed whole exome sequencing of BrazIT and estimated medians of 64%, 17%, and 13% of European, African, and Native American ancestries, respectively, based on autosome SNVs, underscoring the diversity of this cohort. After controlling for covariates, we did not observe association between these continental ancestries and inhibitor titers or ITI success, but Native American ancestry was negatively associated with large deletions in FVIII gene (β = -0.081, p = 0.011). In Latin American populations, sex-ancestry bias is the rule: during the last five centuries, European admixture has been preferentially mediated by males, while African and Native American admixture preferentially by females. We estimated X-chromosome ancestry to confirm the pervasive sex-ancestry bias in BrazIT. As expected, BrazIT individuals show Native American ancestry bias (Autosome - X-chromosome bias: 0.06, p < 0.001), but exceptionally, no African ancestry bias (-0.005, NS). This result suggests that X-chromosomes of predominant African origins are underrepresented among hemophilia patients high-responding inhibitors, exemplifying the unexplored issue of how sex-ancestry bias in Post-Columbian migrations from Europe and Africa to the Americas have differently shaped the patterns of genetic diversity of X-chromosome and autosomal linked mendelian diseases.

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SWITCHING PROPHYLAXIS DURING AN IMMUNE TOLERANCE INDUCTION EVOLVING WITH FAILURE: A CASE REPORT FROM A BRAZILIAN HEMOPHILIA TREATMENT CENTER

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Factor VIII (FVIII) prophylaxis is recommended to prevent bleeds in people with hemophilia A (PwHA). However, up to 30% of severe PwHA (residual plasmatic FVIII activity < 1%) develop anti-FVIII (FVIII) neutralizing antibodies (i.e., inhibitors), leading to ineffectiveness of FVIII replacement and worse outcomes. Immune Tolerance Induction (ITI) is the treatment of choice to eradicate inhibitors, but it demands frequent intravenous infusions and a higher risk of bleeding. Bypassing Agent (BpA) prophylaxis was recommended to avoid bleeding during ITI. Emicizumab is currently available as a prophylactic agent for PwHA and inhibitors, although its impact during ITI is not well described. We reported the effect